SPECIAL SERIES: MATHEMATICAL ONCOLOGY

review article

Blackboard to Bedside: A Mathematical Modeling Bottom-Up Approach Toward Personalized Cancer Treatments

Sara Hamis, MSc[1]; Gibin G. Powathil[1]; and Mark A.J. Chaplain, PhD[2]

abstract

Cancers present with high variability across patients and tumors; thus, cancer care, in terms of disease prevention, detection, and control, can highly benefit from a personalized approach. For a comprehensive personalized oncology practice, this personalization should ideally consider data gathered from various information levels, which range from the macroscale population level down to the microscale tumor level, without omission of the central patient level. Appropriate data mined from each of these levels can significantly contribute in devising personalized treatment plans tailored to the individual patient and tumor. Mathematical models of solid tumors, combined with patient-specific tumor profiles, present a unique opportunity to personalize cancer treatments after detection using a bottom-up approach. Here, we discuss how information harvested from mathematical models and from corresponding in silico experiments can be implemented in preclinical and clinical applications. To conceptually illustrate the power of these models, one such model is presented, and various pertinent tumor and treatment scenarios are demonstrated in silico. The presented model, specifically a multiscale, hybrid cellular automaton, has been fully validated in vitro using multiple cell-line–specific data. We discuss various insights provided by this model and other models like it and their role in designing predictive tools that are both patient, and tumor specific. After refinement and parametrization with appropriate data, such in silico tools have the potential to be used in a clinical setting to aid in treatment protocols and decision making.

PERSONALIZED MEDICINE: A MULTILEVEL APPROACH

Personalized medicine is becoming an increasing part of modern cancer care.[1,2] Patient-specific metrics advise contemporary clinical procedure in terms of vaccine recommendations, screening practice,[3] and treatment planning.[4] The aim of personalized medicine is to tailor health care specifically to the individual patient, in pursuit of optimal treatment outcome and quality of life. As a strategy, personalized medicine can be highly beneficial in cancer care, because cancer is a disease that presents with high variability across incidences. It is indeed well established that a one-to-fit-all strategy to prevent, diagnose, and treat cancer is a subpar approach.[5] Ideally, in line with concepts of personalized medicine, patients should instead be individually evaluated and matched with appropriate cancer care strategies. The personalization of medicine can occur on various levels, as illustrated in Figure 1. Patient and tumor metrics gathered from macrolevel population data down to microlevel molecular tumor data may aid anticancer decision making in a clinical setting.

On a population level, a population can be categorized and divided into various subpopulations, which in turn can be evaluated and risk assessed. Certain subpopulations express elevated risks of developing particular cancer types, and likewise certain subpopulations have a predisposition to aggressive disease. This categorization can be determined by inflexible parameters such as age,[3,4,6,7] genetics,[6,8] ethnicity,[6] and sex,[7] as well as by flexible parameters, such as smoking habits,[9] hormonal exposure,[8] obesity levels,[10] and socioeconomic factors. The combination of wide population data and gathered clinical experience can be used to determine suitable, personalized treatment strategies after tumor detection and also to evaluate the need for cancer screening and vaccine administration.[11] For the individual patient to benefit from screenings, screening scheduling should be personalized to enable optimized cancer intervention.[9] By deploying mathematical models, which incorporate biologic knowledge and evolutionary concepts, optimized and personalized screening recommendations can be achieved.[9] To more competently consider the concerns, quality of life and well-being of a patient, cancer care can be tailored on a patient-specific level. After cancer detection, lifestyle, personal

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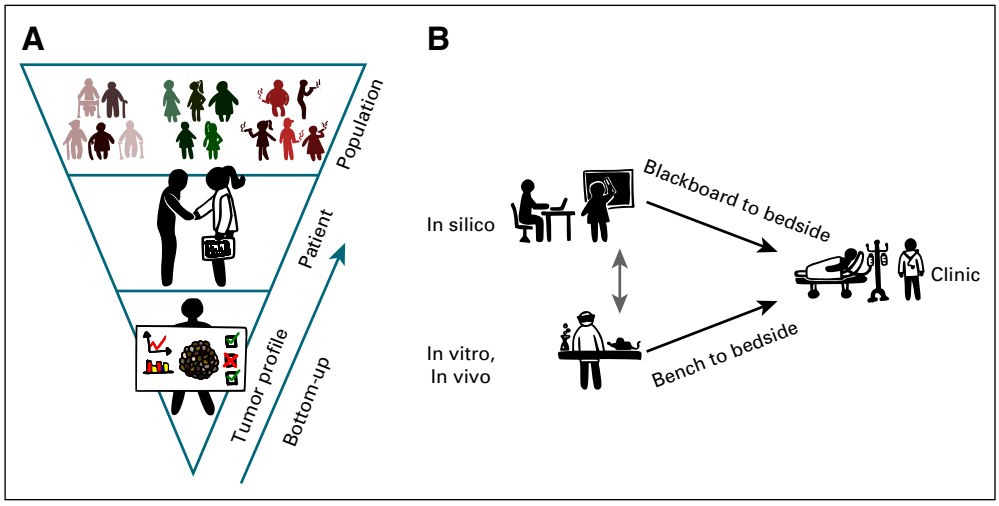

FIG 1. (A) Personalized cancer practice on various levels, namely population, patient, and tumor profile. On a population macrolevel, a population can be categorized into various subpopulations (eg, according to age, sex, or smoking habits), which in turn can be evaluated and risk assessed for preventive, detective and corrective oncology practice. On a central, patient-specific level, cancer care may be tailored to fit the needs, lifestyle, and priorities of the patient, in pursuit of medicine that optimizes both treatment outcome and the patient's quality of life. On a tumor-profile level, tumor-specific data can provide information that may contribute toward disease prognoses and intelligent treatment decisions. Narrowing down cancer care personalization to the tumor level allows for a bottom-up approach to personalized tumor treatments. (B) The bench-to-bedside concept depicts the practice of transferring in vitro and in vivo findings from the laboratory to a clinical setting. The contemporary mathematician works on both blackboards and computer keyboards; thus, we analogously, present the phrase blackboard to bedside to describe the action of translating mathematical and computational intelligences to clinical application.

priorities, and economic factors all contribute toward determination of which treatment strategy is the most appropriate for the individual patient.[6] On this central, patient-specific level of treatment personalization, the dialogue between patient and clinician is of the essence,[6] and it is important that the patient is well informed by the clinician.

In parallel, to keep the clinician as well informed as possible, personalized medicine can be even further detailed and narrowed down to tumor level.[12] After tumor detection, disease forecasting and treatment decisions can be informed by tumor-specific data. Because of the high variability of cancer displayed across disease incidences, previous research indicates that tumor prognoses and treatment responses may correlate more with molecular tumor specifics than with larger-scale factors, such as anatomic tumor origin[1] or metrics quantified on a patient or population level. Recent advances in biomarker handling,[13,14] biopsy techniques, and medical imaging enable tumor assessment[15] before and throughout treatments regimes. However, current biopsy procedures may in certain cases be infeasible to perform, and furthermore, tumors are highly evolutive systems that may rapidly and drastically change after a biopsy. Therefore, being able to predict tumor evolution, progression, and treatment response, given tumor-specific input data at an earlier time point, would present an immensely valuable tool in clinical treatment planning. Recently, via rigorous mathematical modeling of cancer tumors, predictive tumor prognosis is being successfully achieved for virtual tumors.[16] The current mission at hand is to bridge the gap between virtual and physical tumor control so that preclinical and clinical applications will directly benefit from recent advances made in the field of mathematical and computational oncology.

MATHEMATICAL AND COMPUTATIONAL ONCOLOGY

Mathematical and computational oncology has the potential to be especially useful to help personalize clinical cancer practice,[17] because it integrates mathematical and computational approaches with traditional bench and clinical experiments. Because of recent advances in imaging techniques, the vast accumulation of experimental and clinical data, and available computational power, in silico studies have gradually been entering the stage of medical research over the past decades.[18] Cancer is a highly complex disease, and, although this complexity presents difficulties in model formulation, variable parametrization and implementation, this complexity also infers that there is much biomedical insight to be gained from mathematical models and corresponding in silico experiments. Modeling may unveil new, important

information about biologic cancer systems and their submechanisms[19] and thus elucidate underlying tumor processes. The advantages of mathematical and computational oncology are multifold. Compared with other types of experiments, in silico experiments are both cheap and quick to produce,[17] are highly adaptable,[17] and are associated with few ethical concerns. Theories obtained in laboratories or clinics can be tested in silico on virtual tumors before animal testing, so modeling results can be used to guide in vivo experiments.

Today, there exists a wide array of mathematical models that are able to capture various phases of tumor progression and associated mechanisms, such as tumor growth, invasion and metastasis,[20-25] angiogenesis,[26-29] and treatment responses.[30-36] A comprehensive overview of the field may be found in the review article by Lowengrub et al.[37] Some of these models have successfully conferred with both in vitro and in vivo experiments or clinical observations[38-40]; consequently, mathematical tumor modeling is steadily gaining acceptance in the medical community. Recently, several multiscale models have been developed to fully capture the spatiotemporal, multiscale nature of tumor dynamics.[41-44] Such models allow for intratumoral cross-scale integration of intracellular, extracellular, and intercellular concepts, which provides comprehensive modeling frameworks to which new biomedical information can easily be added.

Although advances in cancer research are being made in parallel across many disciplines, multidisciplinary collaborations have the potential to accelerate the process of translating cancer research into successful clinical application. To this end, McGuire et al[45] provide an implementable pipeline for the interdisciplinary development of cancer therapies. They illustrated how to structure the workflow among clinicians, biologists, and researchers from science, technology, engineering, and mathematics in an optimal, feasible manner. The workflow demonstrates how multidisciplinary research should alternate between performance in parallel and sequentially. It also incorporates refining, iterative processes and an outlined order of operations that act to bring new cancer protocols to the clinic as quickly and safely as possible. The concept and workflow proposed by McGuire et al[45] acknowledges, yet transcends, practical limitations, because it allows for collaboration across disciplines, distances, and institutes.

A MULTISCALE MODEL OF SOLID TUMOR DYNAMICS

To demonstrate the great potential of mathematical tumor models, an established hybrid, multiscale model[46] capable of simulating spatiotemporal tumor dynamics under various conditions is presented here in brief. Using this multiscale model, which is implemented with a high performance computational framework, virtual cell populations, or tumors, can be created and various clinical, or preclinical, scenarios can be studied in silico. A handful of selected such scenarios are discussed in the remainder of this paper.

MODEL OVERVIEW AND INTRATUMORAL HETEROGENEITY

The mathematical model presented here is a multiscale, hybrid cellular automaton in which a cancer cell population was simulated on a three-dimensional lattice. It allows for spatiotemporal dynamics and intratumoral heterogeneity and is summarized in Figure 2.[43,46] The model was implemented in an in-house framework based on C++, and cell maps were visualized using ParaView (Kitware, Clifton Park, NY).[47] For a more extensive model description, see previous works by Powathil et al.[43,46] On an intracellular level, each cell was modeled individually to integrate subcellular molecular mechanisms and phenotypical variations among cancer cells. Intracellular cell-cycle progression was modeled by a system of ordinary differential equations on the basis of a regulatory molecular network. The model incorporated extracellular regulations, such as oxygen and drug delivery across the lattice, by mechanistic partial differential equations.

Many cancers are derived from one cancerous seeding cell, which by detection time has produced a tumor with subclonal diversity that displays a few dominant subclones.[50] It has been observed that cells collected from the same tumor may display different subclonal[50] and spatiotemporal features influenced by intracellular, extracellular,[51] and intercellular mechanisms. Consequently, a multitude of tumor metrics will vary within a tumor mass,[14] and this diversity may not be captured by current diagnosis tools.[50] However, in silico experiments provide a platform on which to conveniently study implications of spatiotemporal heterogeneities within a tumor, which thus allows us to study what is not empirically feasible by other methods.

IMPLICATIONS OF INTRATUMORAL OXYGEN PROFILES ON RADIOTHERAPY OUTCOMES

Hypoxic cancer cells express reduced sensitivity to anticancer treatments, such as radiotherapy and some chemotherapeutic drugs.[52] Thus, hypoxia has an adverse effect on treatment delivery and may significantly affect clinical outcome. Consequently, it is important to consider spatiotemporal oxygen dynamics during study, or implementation, of treatment delivery.[49] Accordingly, a previous in silico study by Enderling et al[53] deployed an agent-based model, which accounted for variations in stemness among cancer cells, to emphasize the impact that cancer cell morphology and spatiotemporal heterogeneity has on radiotherapeutic response and hence on success and treatment optimization. Another in silico experiment that considered the hierarchy of tumor-initiating cells was presented by Scott et al[54]; they investigated phenotypic tumor-infiltrating cell features and extrinsic effects on tumor growth using a hybrid cellular automaton. A recent, spatially

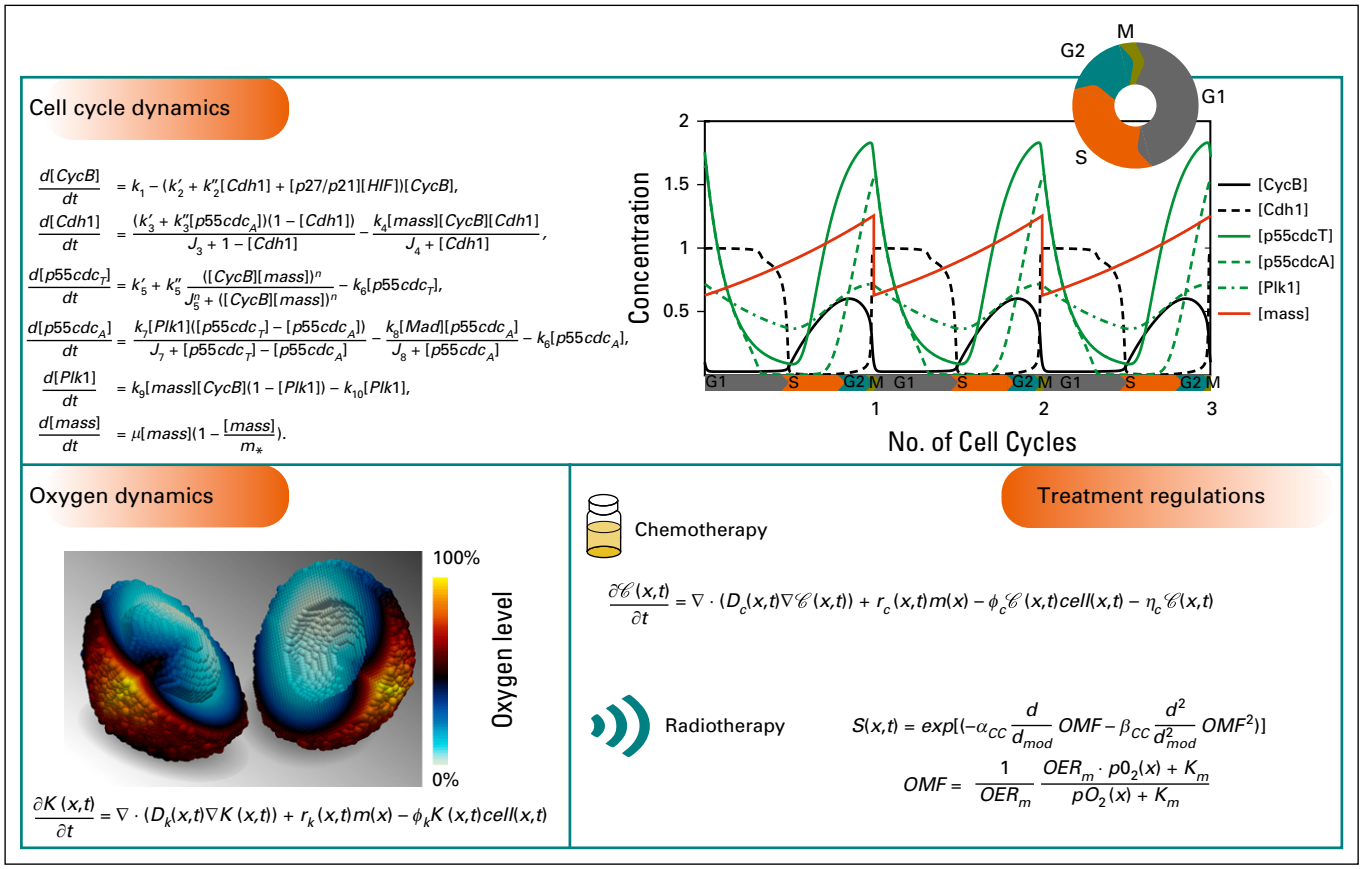

FIG 2. Fundamental mathematical components of the multiscale model. Cell-cycle dynamics are modeled by a system of ordinary differential equations composed of six dependent variables, specifically five protein concentrations and cell mass. Oxygen dynamics obey a mechanistic partial differential equation (PDE). Various treatment regulations are incorporated in the model. Chemotherapy dynamics are modeled by a mechanistic PDE, and radiotherapy response follows the linear-quadratic model. The cellular survival probability $S(x, t)$ after radiation depends on oxygenation status and cell-cycle progression. See Powathil et al[48,49] for additional details.

resolved mathematical study by Lewin et al[55] demonstrated how radiotherapy-induced cell kill alters the intratumoral cell and oxygen composition and, consequently, how a certain tumor's radiotherapy response will vary across a series of administered fractions. In their study, avascular spherical symmetrical tumor growth was modeled by an integrodifferential equation that was coupled with a reaction-diffusion equation that governed oxygen distribution. Radiotherapy response was modeled using the well-established linear-quadratic (LQ) model.

In the presented modeling framework, oxygen dynamics and corresponding consequences were incorporated on multiple scales. Oxygenation status affects a cell's proliferation rate; furthermore, cellular response to radiotherapy is considered to be a function of oxygenation status, cell-cycle advancement, and radiation dosage.[31,46] Figure 3 illustrates how two different virtual tumors (tumor A and tumor B) with different oxygen profiles evolved and responded to radiotherapy. Both tumors stemmed from three identically located seeding cancer cells and were simulated on equisized, three-dimensional lattices. On the lattice that contains tumor A, oxygen was produced on all extracellular lattice points that were not occupied or enclosed by cancer cells. On the second lattice, which correspondingly contains tumor B, oxygen was produced only in one octant of the lattice, as demonstrated in Figure 3. It can be seen that tumor A was significantly more oxygenated than tumor B; consequently, the in silico experiment demonstrated a few key differences between the dynamics of the two tumors. First, the well-oxygenated tumor proliferated faster than the poorly oxygenated tumor, because hypoxia impeded cell-cycle progression. Second, the two tumors displayed different distributions of cellular oxygen levels. Last, radiotherapy was more effective in the well-oxygenated tumor than in the poorly oxygenated tumor. These results demonstrate how useful it can be to consider a detailed tumor profile before treatment planning starts.

CLINICAL RELEVANCE OF RADIATION BYSTANDER EFFECTS

At low radiation doses, the direct effects of delivered radiation are considered relatively low; consequently, the

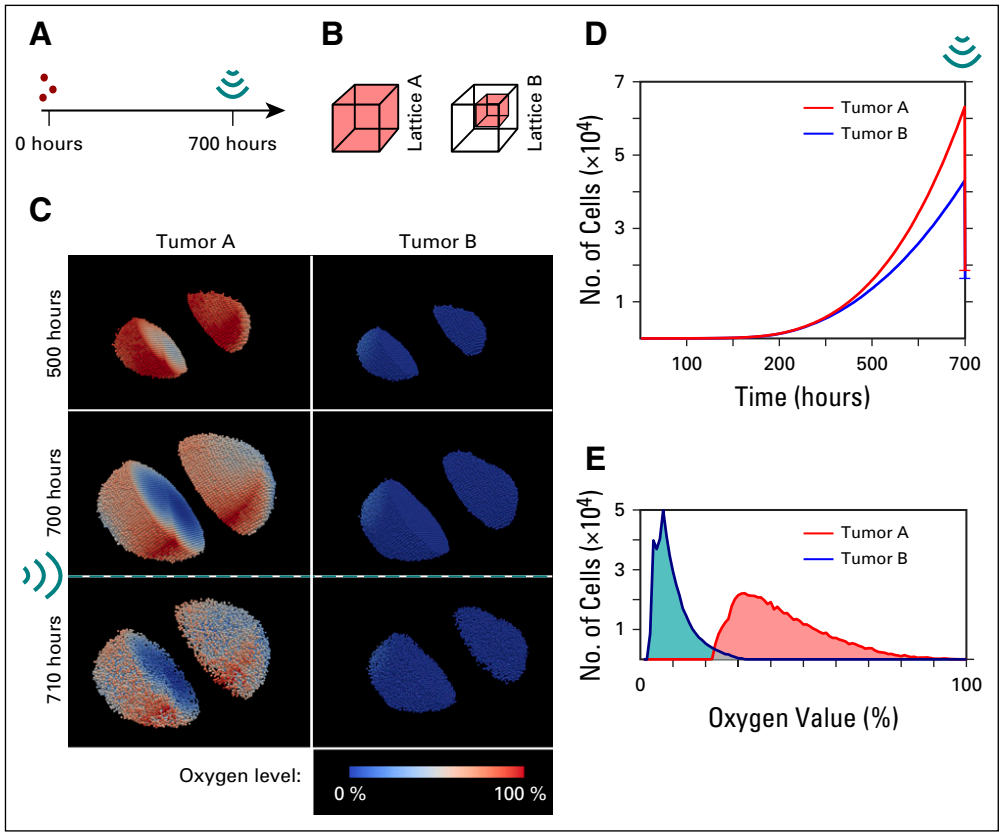

FIG 3. Graphs that illustrate the implication of intratumoral oxygen profiles; cell death by radiation is visualized as instantaneous for clarity. (A) At 0 hours, three seeding cancer cells are planted on a three- dimensional lattice. These cells develop into a tumor that, at 700 hours, is exposed to radiotherapy. (B) Oxygen is produced on all extracellular lattice points in lattice A and on all extracellular lattice points in one octant only in lattice B. (C) Cell maps at 500 and 700 hours (before radiotherapy) and at 710 hours (after radiotherapy) are provided, and colors correspond to cellular oxygenation levels. (D) Graph of tumor growth over time and shrinkage in response to radiotherapy at 700 hours. (E) Intratumoral oxygen distribution at time of radiotherapy administration.

nontargeted effects of radiation play an important role in the determination of cellular radiation response.[48,56,57] In most cases of clinical radiation delivery, the majority of normal tissue adjacent to the targeted tumor is exposed to low-dose radiation in an effort to maximize the dose delivered to the tumor but minimize the damage to surrounding normal structures.[57] Hence, it is important to study the impact of nontargeted effects in clinical radiation therapy and their role in radiation effectiveness and potential radiation-induced carcinogenesis.[57]

Examples of such nontargeted effects include the phenomena known as bystander effects, in which signals produced by irradiated cells influence the behavior of nonirradiated cells.[48,56,58] It is difficult to study these effects independently of direct effects, and, moreover, mediators and targets for bystander signals are poorly understood even after several experimental studies.[49,57,59-64] Recently, several modeling attempts have been made to study and understand radiation bystander effects.[65,66]

In one of these attempts, Powathil et al[66] used a multiscale mathematical modeling framework (Fig 2) to study the impact of radiation and radiation-induced bystander effects on both normal and tumor cells. Here, bystander effects are considered to be produced by bystander signals that diffuse through the medium/microenvironment.[48,59] Radiated and nonirradiated cells that are exposed to these signals are assumed to respond probabilistically, in which varying outcomes, such as cell death, repair delay, and mutation, depend on localized signal intensity. Figures 4A and 4B show the survival fraction of the cells after radiation, with and without bystander-induced cell kill, for two cases of dose delivery.[66] In Figure 4A,[66,67] tumor cells are fully exposed to the given radiation dose, but the surrounding normal cells receive gradients of the dose. In Figure 4B, tumor cells are fully exposed to the given radiation dose, but the surrounding normal cells are spared completely. The plots show that, at low doses (< 0.5 Gy), bystander effects contribute to a higher cell kill than do direct effects. This indicates that bystander effects might play a role in low-dose radiation hypersensitivity, as observed in multiple experimental studies, such as one shown in Figure 4C (which compares curves for the LQ model and the LQ model with bystander effects). These in silico results are also confirmed with experiments by Fernandez et al.[59]

DRUG RESISTANCE AND DRUG RESPONSE

After chemotherapy, tumor recurrence is a prevalent clinical problem, and reappearing cancers are often observed to be increasingly drug resistant. Cancer cells may possess, acquire, and communicate drug-resistant traits, which enable them to survive under otherwise lethal conditions, after exposure to chemotherapeutic drugs. The

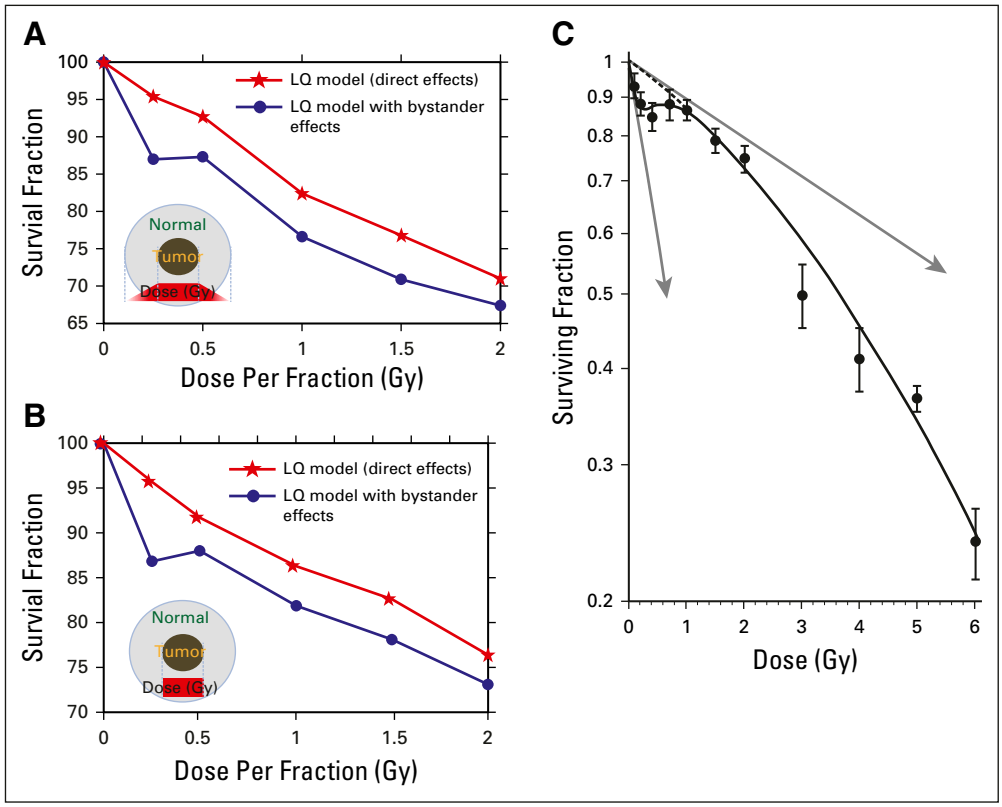

FIG 4. Plots that show radiation bystander effects and the difference in cellular survival fraction when bystander responses are considered. (A) Tumor cells are fully exposed to the given radiation dose, whereas the surrounding normal cells receive a gradient of the dose. (B) Tumor cells are exposed to the fully given radiation dose, whereas the surrounding normal cells are spared completely. (C) Experimental result: survival of asynchronous T98G human glioma cells irradiated with 240 kVp x-rays, measured using the cell-sort protocol. Used with Elsevier permission from Joiner et al[35] and adapted from Powathil et al.[58]

efficacy of chemotherapy treatments is significantly influenced by drug-resistant traits expressed by the targeted tumor.

Tumor dynamics in cancer cell populations that display drug-resistant traits, derived from inheritance or mutations, which are spontaneous, drug-induced or communicated via exosomes, can be studied in silico.[68] The coexistence of drug-resistant and drug-sensitive cells yields a competition between subpopulations, and the evolution and ecology of cancer cell populations obey Darwinian rules.[69] It has been demonstrated that drug-resistant subpopulations are more fit to survive in the presence of drugs, whereas drug-sensitive cells are more fit to survive in the absence of drugs. This is in accordance with the argument that cells may indeed acquire drug resistance as a survival endeavor; however, by doing so, other cellular driving mechanisms are compromised.[69] To study these concepts in silico, we here investigated tumor growth and chemotherapy response of a tumor composed of two subpopulations, one of which was sensitive to drugs and one of which was drug resistant. The drug-resistant subpopulation was immune to drug effects but had reduced proliferation ability, specifically a cell-cycle length of roughly twice that of the sensitive subpopulation. At the start of the in silico experiment, one drug-sensitive and one drug-resistant cell were placed on the lattice. As is clearly demonstrated in Figure 5, the sensitive subpopulation dominated in size before drug administration because of its higher proliferation rate. Drugs, specifically cisplatin, were administered at 700 and 800 hours in a single or double dosage. The results demonstrated how the choice of drug dosage influences the outcome of chemotherapy. Although a higher drug dosage killed more cancerous cells, it also altered the composition of sensitive-to-resistant cells in favor of the drug-resistant subpopulation. Repeated use of such chemotherapy administration would quickly render the tumor uncontrollable by chemotherapy. This conceptually shows that suboptimal chemotherapy administration may contribute toward drug resistance. In other words, chemotherapy that does not kill a tumor may make it stronger.[68]

Traditionally, the goal of clinical chemotherapy has been to reduce the tumor size as much as possible with minimal toxicity. However, Hamis et al[68] recently demonstrated that chemotherapy treatments, in terms of dosage administration and scheduling, should be tumor specific to simultaneously suppress tumor size and drug-resistant tumor features.[68] A treatment strategy backed up by mathematical modeling is adaptive chemotherapy,[69] which takes advantage of the competition between drug-sensitive and drug-resistant subpopulations in an effort to improve treatment outcomes. This promising, and mathematically validated, strategy does however imply breaking free from the clinically traditional set-dosage, set-schedule practice. This shows that mathematical models, such as the one described here, can be useful to motivate, develop, and

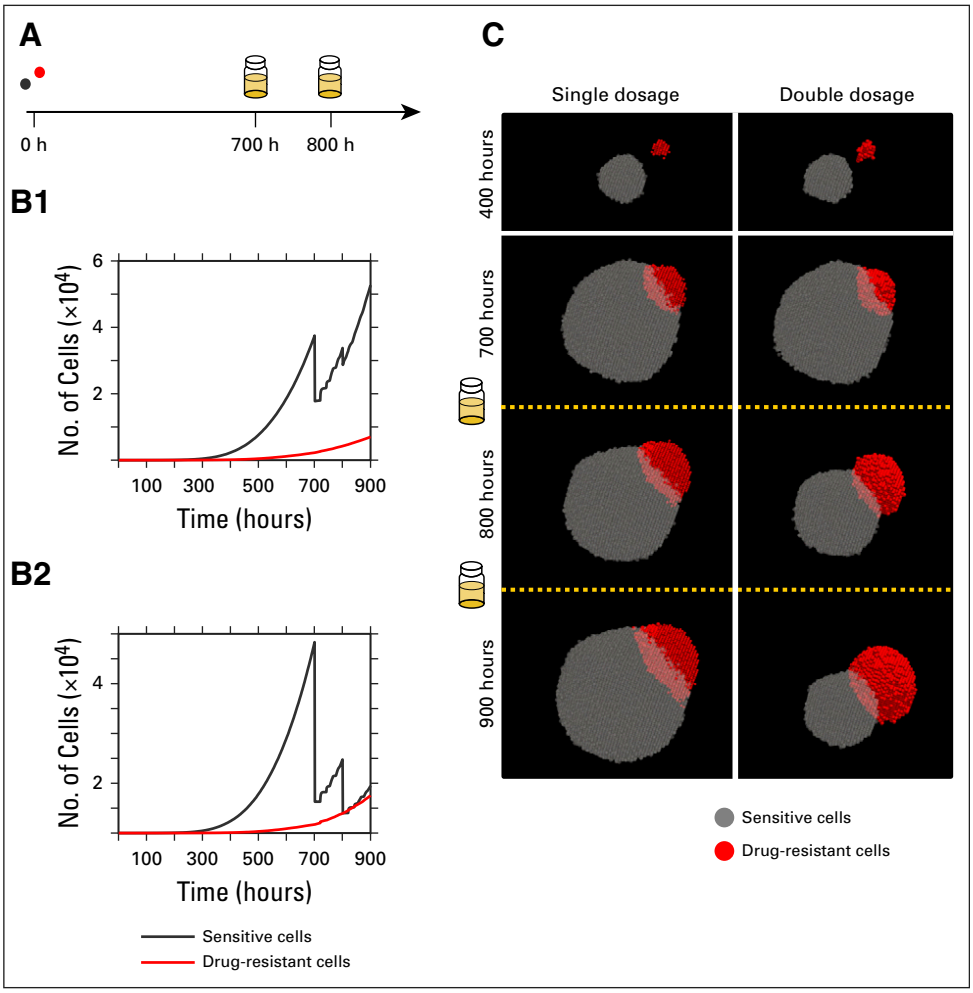

FIG 5. Graphs that illustrate drug resistance and drug response, in which cells are visualized as euthanized instantaneously for clarity. (A) At 0 hours, one sensitive and one drug resistant cell is placed on the lattice and drugs are instantaneously administered at 700 and 800 hours. (B) Number of cells over time for a single (1) and double (2) drug dosage. (C) Cell maps at 400, 700, 800, and 900 hours.

guide personalized treatment protocols informed by available data.

HYPOXIA-ACTIVATED PRODRUGS

Because of recognized implications of hypoxia, multiple strategies to combat hypoxia have been explored.[70] Hypoxia-activated prodrugs (HAPs) present a means to not only combat, but better yet, exploit hypoxia in anticancer therapies.[52] HAPs comprise bioreductive prodrugs that reduce to active cytotoxins upon reaching hypoxic regions.[64,71,72] Because tumors, as a rule, express levels of hypoxia of higher severity than do other relevant tissues in the host system, tumors can be targeted. HAPs may thus operate as trojan horses, which are essentially harmless until they are converted in targets—in other words, hypoxic tumors regions. Combination treatments of HAPs and ionizing radiation have produced optimistic preclinical results,[72] but, despite the conceptual promise of HAPs, clinical trials of HAPs have produced mixed outcomes. Mathematical modeling can help elucidate the (somewhat disheartening) results of clinical HAP trials.

Previous mathematical studies have already contributed to the overall understanding of HAPs. Work by Foehrenbacher et al[73] quantified bystander effects elicited by the HAP PR-104 using a Green's function method, in customized form, and pharmacokinetic/pharmacodynamic modeling. Similar mathematical concepts were used in a later study to compare class I HAPs with class II HAPs and to determine optimal properties for class II HAPs.[74] TH-302 is a HAP that has been tested for an array of cancers in clinical trials. Using a stochastic model, Lindsay et al[75] studied TH-302–erlotinib monotherapies and combination therapies to conclude that a combination therapy of the two drugs impedes the uprising of drug resistance. HAPs bioreduce to activated form under hypoxic conditions, so a previous study by Wojtkowiak et al[76] investigated, and conceptually validated, the strategy of deliberately exacerbating intratumoral hypoxia using exogenous pyruvate to amplify TH-302 activity. Their study combined metabolic profiling and electron paramagnetic resonance imaging with mathematical modeling, in which HAP dynamics was modeled using reaction-diffusion/convection equations coupled with fluid-structure interactions.

Here, we extended the multiscale framework summarized in Figure 2 to study HAP dynamics and appropriate tumor conditions for HAP success. In the model, HAPs were

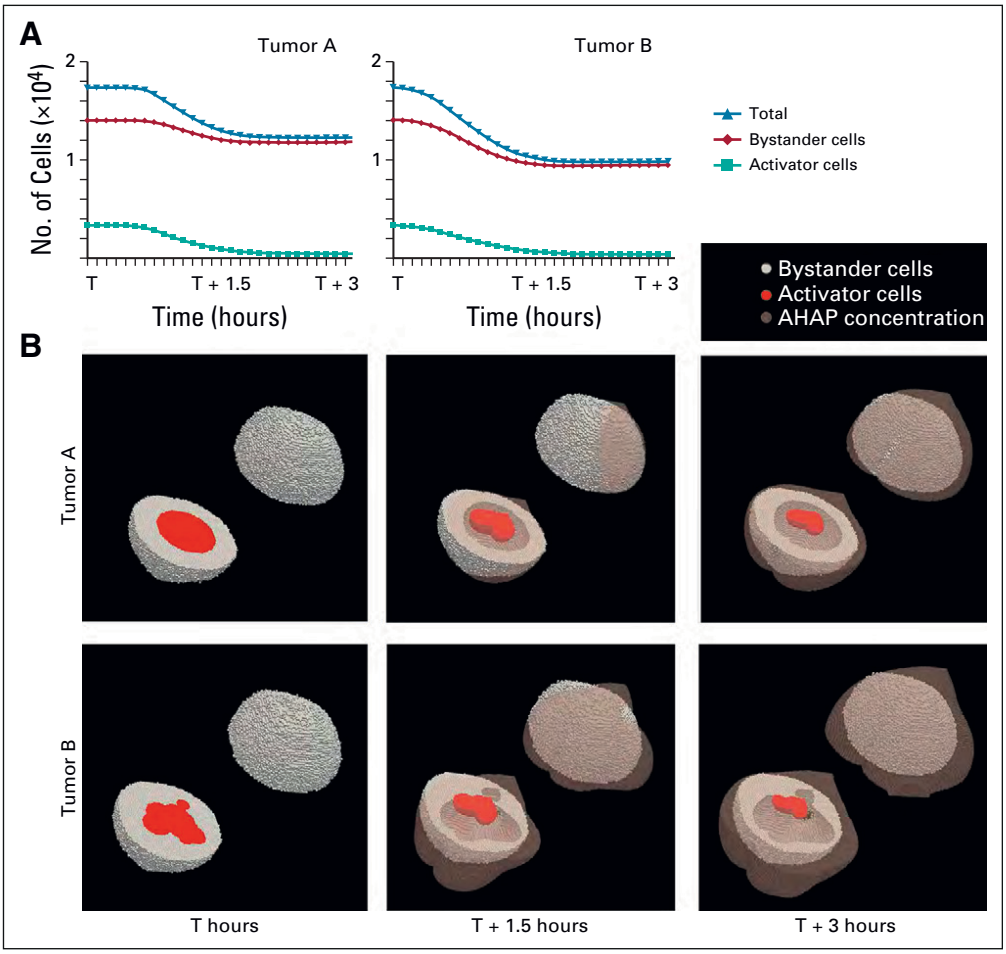

FIG 6. The effect of hypoxia-activated prodrugs, in which cell death is visualized as instantaneous for clarity. (A) Number, and total, of activator and bystander cells during hypoxia-activated prodrug treatment of tumors A and B. (B) Cell maps of tumors A and B at the time of treatment (T), 1.5 hours after the treatment (T + 1.5), and 3 hours after the treatment (T + 3). AHAP, activated form of hypoxia-activated prodrugs.

assumed to follow similar dynamics as that of chemotherapy, in which HAPs bioreduced to activated form (ie, AHAPs) after they were on a sufficiently hypoxic lattice point. Cells that were hypoxic enough to activate the prodrug are called activators, and other cancer cells are bystander cells. Both activators and bystander cells may be euthanized by the DNA linking effect of AHAPs. Figure 6 illustrates an in silico experiment in which two tumor spheroids, tumor A and tumor B, are subjected to HAPs. Both tumors consisted of 20% activator cells. In tumor A, the activator cells were concentrically located in the center of the tumor spheroid, but the activator cells in tumor B were scattered in clusters. The results indicate that, despite the fact that tumor A and tumor B contained the same number of activator and bystander cells, HAPs were more effective in tumor B than in tumor A. This demonstrates that not only the hypoxic tumor fraction but also the spatiotemporal distribution of hypoxic cells may influence HAP efficacy. Tumor-specific treatment personalization is, again, of the essence, because the results demonstrate that the successfulness of HAP treatments strongly correlates with tumor-specific features. This indicates that, in a clinical setting, patients might need to be carefully selected for HAP treatments via sufficiently comprehensive tumor assessments.

DISCUSSION

Mathematical modeling has chronologically tailed clinical implementation of tumor treatment strategies. Historically, this time lag is validated in the early era of modern cancer care practice, which preceded advanced technology. However, with current imaging and biopsy technologies; sophisticated in vitro and in vivo laboratories; accumulating data from experiments and clinics; available computational power[18]; and biologic, medical, and mathematical knowledge, mathematical oncology today constitutes an up-to-date complement to traditional cancer research. Modeling has the potential to both optimize currently available anticancer protocols and contemporaneously aid preclinical developments of new anticancer therapies. Thus, the time lag between clinical applications and mathematical modeling is conceptually being eliminated. However, to comprehensively transfer insights from blackboard to bedside, actualized collaboration between clinicians and mathematicians, as well as between biologists and experimentalists, is key.[77]

In this article, we demonstrated how mathematical tumor models can be used to study pertinent treatment scenarios in silico. Once validated, data driven, predictive mathematical models can eventually help plan

personalized treatment protocols by acting as in silico test bases. For a more complete translation of intelligence from blackboard-to-bedside, there exists a need to integrate tumor-host interactions mathematically. However, cell population models, such as those described here, constitute a crucial stepping stone to realization of a bottom-up approach toward personalized medicine.

AFFILIATIONS

[1]Swansea University, Swansea, Wales, United Kingdom
[2]University of St Andrews, St Andrews, Scotland, United Kingdom

CORRESPONDING AUTHOR

Mark A.J. Chaplain, MD, University of St Andrews School of Medicine, North Haugh, St Andrews, Fife KY16 9SS, Scotland, United Kingdom; Twitter: @ mcapellanus and @univofstandrews; e-mail: majc@st-andrews.ac.uk.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Collection and assembly of data: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Jackson SE, Chester JD: Personalised cancer medicine. Int J Cancer 137:262-266, 2015
2. Lawler M, Sullivan R: Personalised and precision medicine in cancer clinical trials: Panacea for progress or Pandora's box? Public Health Genomics 18:329-337, 2015
3. Roussel C, Touboul C: Large population survey: Strengths and limits—Methodology of the EDIFICE survey. Eur J Cancer Prev 20:S5-S7, 2011
4. Dumontet C, Couray-Targe S, Teisseire M, et al: Real life management of patients hospitalized with multiple myeloma in France. PLoS One 13:e0196596, 2018
5. Turnbull AK: Personalized medicine in cancer: Where are we today? Future Oncol 11:2795-2798, 2015
6. Burke W, Brown Trinidad S, Press NA: Essential elements of personalized medicine. Urol Oncol 32:193-197, 2014
7. Moutel G, Duchange N, Darquy S, et al: Women's participation in breast cancer screening in France: An ethical approach. BMC Med Ethics 15:64, 2014
8. Brédart A, Kop JL, Antoniou AC, et al: Clinicians' use of breast cancer risk assessment tools according to their perceived importance of breast cancer risk factors: An international survey. J Community Genet, 2018
9. Curtius K, Wright NA, Graham TA: An evolutionary perspective on field cancerization. Nat Rev Cancer 18:19-32, 2018
10. Duong MN, Geneste A, Fallone F, et al: The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance. Oncotarget 8:57622-57641, 2017
11. Hu Z, Ott PA, Wu CJ: Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nat Rev Immunol 18:168-182, 2018
12. Tremblay-Servier M: Personalized medicine: The medicine of tomorrow. Metabolism 62:S1, 2013
13. Buil-Bruna N, Sahota T, López-Picazo JM, et al: Early prediction of disease progression in small cell lung cancer: Toward model-based personalized medicine in oncology. Cancer Res 75:2416-2425, 2015
14. Gay L, Baker AM, Graham TA: Tumour cell heterogeneity. F1000 Res 5:5, 2016
15. Yankeelov TE, An G, Saut O, et al: Multi-scale modeling in clinical oncology: Opportunities and barriers to success. Ann Biomed Eng 44:2626-2641, 2016
16. Rejniak KA, Lloyd MC, Reed DR, et al: Diagnostic assessment of osteosarcoma chemoresistance based on virtual clinical trials. Med Hypotheses 85:348-354, 2015
17. Karolak A, Markov DA, McCawley LJ, et al: Towards personalized computational oncology: From spatial models of tumour spheroids, to organoids, to tissues. J R Soc Interface 15:20170703, 2018
18. Geris L: Regenerative orthopaedics: In vitro, in vivo...in silico. Int Orthop 38:1771-1778, 2014
19. Mardinoglu A, Nielsen J: Systems medicine and metabolic modelling. J Intern Med 271:142-154, 2012
20. Andasari V, Gerisch A, Lolas G, et al: Mathematical modeling of cancer cell invasion of tissue: Biological insight from mathematical analysis and computational simulation. J Math Biol 63:141-171, 2011
21. Benzekry S, Lamont C, Beheshti A, et al: Classical mathematical models for description and prediction of experimental tumor growth. PLOS Comput Biol 10:e1003800, 2014
22. Byrne HM, Chaplin MA: Growth of necrotic tumors in the presence and absence of inhibitors. Math Biosci 135:187-216, 1996
23. Gerisch A, Chaplain MA: Mathematical modelling of cancer cell invasion of tissue: Local and non-local models and the effect of adhesion. J Theor Biol 250:684-704, 2008
24. Ramis-Conde I, Chaplain MA, Anderson AR, et al: Multi-scale modelling of cancer cell intravasation: The role of cadherins in metastasis. Phys Biol 6:016008, 2009
25. Ramis-Conde I, Drasdo D, Anderson AR, et al: Modeling the influence of the E-cadherin-beta-catenin pathway in cancer cell invasion: A multiscale approach. Biophys J 95:155-165, 2008
26. Anderson AR, Chaplain MA: Continuous and discrete mathematical models of tumor-induced angiogenesis. Bull Math Biol 60:857-899, 1998
27. Macklin P, McDougall S, Anderson AR, et al: Multiscale modelling and nonlinear simulation of vascular tumour growth. J Math Biol 58:765-798, 2009

28. McDougall SR, Anderson AR, Chaplain MA: Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: Clinical implications and therapeutic targeting strategies. J Theor Biol 241:564-589, 2006
29. Suzuki T, Minerva D, Nishiyama K, et al: Study on the tumor-induced angiogenesis using mathematical models. Cancer Sci 109:15-23, 2018
30. Agur Z, Hassin R, Levy S: Optimizing chemotherapy scheduling using local search heuristics. Oper Res 54:829-846, 2006
31. Enderling H, Chaplain MA, Hahnfeldt P: Quantitative modeling of tumor dynamics and radiotherapy. Acta Biotheor 58:341-353, 2010
32. Fister KR, Panetta JC: Optimal control applied to cell-cycle-specific cancer chemotherapy. SIAM J Appl Math 60: 1059-1072, 2000
33. Leder K, Pitter K, LaPlant Q, et al: Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. Cell 156:603-616, 2014
34. Ribba B, Colin T, Schnell S: A multiscale mathematical model of cancer, and its use in analyzing irradiation therapies. Theor Biol Med Model 3:7, 2006
35. Ribba B, Marron K, Agur Z, et al: A mathematical model of doxorubicin treatment efficacy for non-Hodgkin's lymphoma: Investigation of the current protocol through theoretical modelling results. Bull Math Biol 67:79-99, 2005
36. Rockne R, Alvord EC, Szeto M, et al: Modeling Diffusely Invading Brain Tumors: An Individualized Approach to Quantifying Glioma Evolution and Response to Therapy. Selected Topics in Cancer Modeling. Boston, MA, Birkhauser, 2008
37. Lowengrub JS, Frieboes HB, Jin F, et al: Nonlinear modelling of cancer: Bridging the gap between cells and tumours. Nonlinearity 23:R1-R9, 2010
38. Billy F, Ribba B, Saut O, et al: A pharmacologically based multiscale mathematical model of angiogenesis and its use in investigating the efficacy of a new cancer treatment strategy. J Theor Biol 260:545-562, 2009
39. Bruningk S, Powathil G, Ziegenhein P, et al:Combining radiation with hyperthermia: A multiscale model informed by in vitro experiments. J R Soc Interface 15:20170681, 2018
40. Byrne HM: Dissecting cancer through mathematics: From the cell to the animal model. Nat Rev Cancer 10:221-230, 2010
41. Alarcon T, Byrne HM, Maini PK: A multiple scale model for tumour growth. Multiscale Model Simul 3:440-475, 2005
42. Deisboeck TS, Wang Z, Macklin P, et al: Multiscale cancer modeling. Annu Rev Biomed Eng 13:127-155, 2011
43. Powathil GG, Gordon KE, Hill LA, et al: Modelling the effects of cell-cycle heterogeneity on the response of a solid tumour to chemotherapy: Biological insights from a hybrid multiscale cellular automaton model. J Theor Biol 308:1-19, 2012
44. Zhang L, Wang Z, Sagotsky JA, et al: Multiscale agent-based cancer modeling. J Math Biol 58:545-559, 2009
45. McGuire MF, Enderling H, Wallace DI, et al: Formalizing an integrative, multidisciplinary cancer therapy discovery workflow. Cancer Res 73:6111-6117, 2013
46. Powathil GG, Swat M, Chaplain MA: Systems oncology: Towards patient-specific treatment regimes informed by multiscale mathematical modelling. Semin Cancer Biol 30:13-20, 2015
47. Ayachit U: The ParaView Guide: A Parallel Visualization Application. Kitware, New York, NY, 2015
48. Prise KM, O'Sullivan JM: Radiation-induced bystander signalling in cancer therapy. Nat Rev Cancer 9:351-360, 2009
49. Azzam EI, de Toledo SM, Waker AJ, et al: High and low fluences of alpha-particles induce a G1 checkpoint in human diploid fibroblasts. Cancer Res 60:2623-2631, 2000
50. Valent P, Bonnet D, Wöhrer S, et al: Heterogeneity of neoplastic stem cells: Theoretical, functional, and clinical implications. Cancer Res 73:1037-1045, 2013
51. Rodic S, Vincent MD: Reactive oxygen species (ROS) are a key determinant of cancer's metabolic phenotype. Int J Cancer 142:440-448, 2018
52. Denny WA: The role of hypoxia-activated prodrugs in cancer therapy. Lancet Oncol 1:25-29, 2000
53. Enderling H., Park D., Hlatky L., et al: The importance of spatial distribution of stemness and pro- liferation state in determining tumor radioresponse. Math Model Nat Phenom 4:117-133, 2009
54. Scott JG, Hjelmeland AB, Chinnaiyan P, et al: Microenvironmental variables must influence intrinsic phenotypic parameters of cancer stem cells to affect tumourigenicity. PLOS Comput Biol 10:e1003433, 2014
55. Lewin TD, Maini PK, Moros EG, et al: The evolution of tumour composition during fractionated radiotherapy: Implications for outcome. Bull Math Biol 80:1207-1235, 2018
56. Mothersill C, Seymour CB: Radiation-induced bystander effects: Implications for cancer. Nat Rev Cancer 4:158-164, 2004
57. Munro AJ: Bystander effects and their implications for clinical radiotherapy. J Radiol Prot 29A133-A142, 2009 (suppl 2A)
58. Blyth BJ, Sykes PJ: Radiation-induced bystander effects: What are they, and how relevant are they to human radiation exposures? Radiat Res 176:139-157, 2011
59. Fernandez-Palomo C, Mothersill C, Bräuer-Krisch E, et al: γ-H2AX as a marker for dose deposition in the brain of wistar rats after synchrotron microbeam radiation. PLoS One 10:e0119924, 2015
60. Lorimore SA, McIlrath JM, Coates PJ, et al: Chromosomal instability in unirradiated hemopoietic cells resulting from a delayed in vivo bystander effect of gamma radiation. Cancer Res 65:5668-5673, 2005
61. Lyng FM, Seymour CB, Mothersill C: Production of a signal by irradiated cells which leads to a response in unirradiated cells characteristic of initiation of apoptosis. Br J Cancer 83:1223-1230, 2000
62. Mothersill C, Seymour CB: Bystander and delayed effects after fractionated radiation exposure. Radiat Res 158:626-633, 2002
63. Seymour CB, Mothersill C: Relative contribution of bystander and targeted cell killing to the low-dose region of the radiation dose-response curve. Radiat Res 153:508-511, 2000
64. Sun JD, Liu Q, Ahluwalia D, et al: Comparison of hypoxia-activated prodrug evofosfamide (TH-302) and ifosfamide in preclinical non-small cell lung cancer models. Cancer Biol Ther 17:371-380, 2016
65. Poleszczuk J, Krzywon A, Forys U, et al: Connecting radiation-induced bystander effects and senescence to improve radiation response prediction. Radiat Res 183:571-577, 2015
66. Powathil GG, Munro AJ, Chaplain MA, et al: Bystander effects and their implications for clinical radiation therapy: Insights from multiscale in silico experiments. J Theor Biol 401:1-14, 2016
67. Joiner MC, Marples B, Lambin P, et al: Low-dose hypersensitivity: Current status and possible mechanisms. Int J Radiat Oncol Biol Phys 49:379-389, 2001
68. Hamis S, Nithiarasu P, Powathil GG: What does not kill a tumour may make it stronger: In silico insights into chemotherapeutic drug resistance. J Theor Biol 454:253-267, 2018
69. Gatenby R, Brown J: The evolution and ecology of resistance in cancer therapy. Cold Spring Harb Perspect Med 8:a033415, 2018
70. Sun JD, Liu Q, Wang J, et al: Selective tumor hypoxia targeting by hypoxia-activated prodrug TH-302 inhibits tumor growth in preclinical models of cancer. Clin Cancer Res 18:758-770, 2012
71. Phillips RM: Targeting the hypoxic fraction of tumours using hypoxia-activated prodrugs. Cancer Chemother Pharmacol 77:441-457, 2016

72. Peeters SG, Zegers CM, Biemans R, et al: TH-302 in combination with radiotherapy enhances the therapeutic outcome and is associated with pretreatment [^{18}F]HX4 hypoxia PET imaging. Clin Cancer Res 21:2984-2992, 2015
73. Foehrenbacher A, Patel K, Abbattista MR, et al: The role of bystander effects in the antitumor activity of the hypoxia-activated prodrug PR-104. Front Oncol 3:263, 2013
74. Foehrenbacher A, Secomb TW, Wilson WR, et al: Design of optimized hypoxia-activated prodrugs using pharmacokinetic/pharmacodynamic modeling. Front Oncol 3:314, 2013
75. Lindsay D, Garvey CM, Mumenthaler SM, et al: Leveraging hypoxia-activated prodrugs to prevent drug resistance in solid tumors. PLOS Comput Biol 12:e1005077, 2016
76. Wojtkowiak JW, Cornnell HC, Matsumoto S, et al: Pyruvate sensitizes pancreatic tumors to hypoxia-activated prodrug TH-302. Cancer Metab 3:2, 2015
77. Lawler M, Selby P, Wright JC: Personalized cancer medicine: Are we there yet? Oncologist 18:649-650, 2013